This document was submitted to EPA by a registrant in connection with EPA's evaluation of this chemical, and it is presented here exactly as submitted.

March 20, 2000

SUMMARY AND SIGNIFICANCE OF THE RESULTS FROM THE PATHOLOGY WORKING GROUP PEER REVIEW OF PROLIFERATIVE LESIONS OF THE LIVER IN FEMALE RATS IN A 24-MONTH ORAL TOXICITY/ONCOGENICITY STUDY OF MALATHION (MRID 43942901)

PATHOLOGY REVIEW AND REEVALUATION

1. At the request of Cheminova A/S, a pathology peer review (PPR) has been conducted of all liver slides from female F-344 rats from the 1996 chronic toxicity /oncogenicity study with malathion (MRID 43942901). Dr. William Busey of Experimental Pathology Laboratories, Inc. conducted the PPR, on March 14, 2000 at Huntingdon Life Sciences (HLS) in East Millstone, New Jersey. Dr. Henry Bolte, the original study pathologist (SP), was present at the PPR.

2. A Pathology Working Group (PWG) consisting of Drs. Jerry Hardisty (Chair), Paul Hildebrandt, Robert Garman and Michael Elwell along with Drs. Busey and Bolte, was convened on March 15, 2000 at the same location. Attending as observers were Dr. Don O'Shaughnessy (Cheminova, Inc.) and Dr. Judith Hauswirth and Mrs. Meena Sonawane (both from Jellinek, Schwartz & Connolly, Inc.). The U.S. EPA declined to accept Cheminova's invitation to send an observer.

3. The PWG was conducted in full compliance with the procedures described in PR Notice 94-5 (August 24, 1994). All slides containing sections previously diagnosed by the SP or the PPR as hepatocellular carcinoma or adenoma or as indicating various degrees of severity of non-neoplastic proliferative lesions (foci of cellular alteration and/or hypertrophy/hyperplasia) were examined. All slides were coded so that the PWG was blinded to the treatment groups. The PWG diagnoses were unanimous with regard to every slide but one. The exception was that for one animal, one PWG pathologist believes that the liver contained a hepatocellular adenoma, while the other four believe it was an area of hepatocellular alteration.(non neoplastic lesion). No changes in diagnoses were made after the slides were decoded.

4. The results of the PWG evaluation compared with the original diagnoses by the SP are shown below in Table 1. The historical control data from NTP and HLS are shown below in Table 2.

Table 1. Incidence of liver tumors in female rats before and after PWG review.

Tumor Type	Dose Levels (ppm)									
	0		100/50		500		6,000		12,000	
	SP	PWG	SP	PWG	SP	PWG	SP	PWG	SP	PWG
No. of Animals	70	70	55	55	55	55	55	55	70	70
Hepatocellular Adenoma	0	**0**	1	**1**	1	**2**	3	**0**	3	**5**
Hepatocellular Carcinoma	0	**0**	1	**0**	1	**0**	0	**0**	3	**0**
Combined	0	**0**	2	**1**	2	**2**	3	**0**	6	**5**
% Incidence	0%	**0%**	3.6%	**1.8%**	3.6%	**3.6%**	5.5%	**0%**	8.6%	**7.1%**

SP = Study pathologist results PWG = PWG review results

Table 2. Historical Control Data (Hepatocellular Tumors in Female F344 Rats)

Type of Tumor	NTP		HLS	
	Mean	Range	Mean	Range
Hepatocellular Adenoma	2.3%	0-10% (N = 1900)	1.6%	0-5.4% (n = 254)
Hepatocellular Carcinoma	0.2%	0-2% (n = 1900)	1.1%	0-2.4% (n = 254)

The most significant changes are as follows:

- The PWG concluded that there were no hepatocellular carcinomas at any dose level;
- There were fewer benign adenomas than initially diagnosed by the study pathologist in the 100/50, 500 and 6,000 ppm groups (1, 2 and 0, respectively). The PWG concluded that none of these were related to treatment. Furthermore, the incidence of these tumors is within the historical control value for the laboratory; and
- At the highest dose level employed (12,000 ppm), the PWG concluded there were five benign adenomas compared with the three originally identified by the SP. This resulted from the PWG:
  - diagnosing the three carcinomas diagnosed by the SP to be adenomas,
  - confirming one adenoma diagnosed by the SP to be an adenoma,
  - diagnosing one adenoma that was diagnosed by the SP to be a hepatocellular alteration,
  - diagnosing one hepatocellular alteration diagnosed by the SP to be an adenoma, and
  - diagnosing one adenoma that was diagnosed by the SP to be a non proliferative lesion.

5. Based on the results of the PWG review, Cheminova believes that, in the 1996 chronic rat toxicity/oncogenicity study with malathion, there was no evidence of hepatocellular carcinoma at any dose level and no evidence of an increased incidence of hepatocellular adenomas at dose levels below 12,000 ppm. Furthermore, Cheminova agrees with CARC's conclusion that there was excessive toxicity at the 12,000 ppm dose level and that all tumors observed in this dose group should be disregarded for purposes of risk assessment.

REGULATORY IMPLICATIONS OF PWG REPORT

1. The Cancer Assessment Review Committee (CARC) classification of malathion as a "likely human carcinogen" is based primarily on the SP's original conclusions that liver tumors (adenomas and carcinomas) were present in female rats at doses that were not considered excessive (i.e., below 12,000 ppm). Because the PWG determined that there are no carcinomas at any dose level, there are no adenomas in the 6,000 ppm dose group, and at

lower dose levels there is no relationship of adenomas to treatment, Cheminova believes that there is no scientifically sound basis for CARC's classification of malathion as a "likely human carcinogen".

2. The basis of CARC's proposed human risk assessment was a cancer potency factor (Q_1*) calculated from the incidence of benign liver adenomas. Of central importance in this calculation were the three adenomas originally diagnosed by the SP at 6,000 ppm. The fact that the PWG found no adenomas at the 6,000 ppm dose level and no treatment-related adenomas at any dose level that was not excessive, renders any calculation of a Q_1* statistically and biologically meaningless.

3. Cheminova believes that the PWG findings require the CARC to reconsider its classification of malathion as a "likely human carcinogen".

4. Cheminova believes that the weight of the evidence, including the results of the PWG, suggest that malathion should be classified as a "not likely to be carcinogenic to humans".